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APPLICATION NUMBER: 10/652,634

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RELATED PCT APPLICATION NUMBER: PCT/US04/26607

Certified by

Jon W Dudas

Acting Under Secretary of Commerce  
for Intellectual Property  
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NEW APPLICATION TRANSMITTAL



Transmitted herewith for filing is the patent application of  
Inventors: Old et al

For: CYCLOHEXYL PROSTAGLANDIN ANALOGS AS EP<sub>1</sub>-RECEPTOR AGONISTS

1. TYPE OF APPLICATION

This new application is for a

- ☒ Original
- ☐ Divisional
- ☐ Continuation-In-Part (CIP)
- ☐ \_\_\_\_\_

2. PAPERS ENCLOSED WHICH ARE REQUIRED FOR FILING DATE UNDER 37 CFR 1.53(B) (REGULAR) OR 37 CFR 1.153 (DESIGN) APPLICATION

- 35 Pages of specification
- 9 Pages of claims
- 1 Pages of Abstract
- 6 Sheets of Drawing
  - ☒ formal
  - ☐ informal
- \_\_\_\_\_ A copy of the original patent application, including Claims and the Declaration and Power of Attorney

3. ADDITIONAL PAPERS ENCLOSED

- ☐ Preliminary Amendment
- ☒ Information Disclosure Statement
- ☒ Form PTO-1449 and references
- ☐ Other: Version with markings to show changes made (1 pg.)

4. ASSIGNMENT

- ☒ An assignment of the invention to Allergan, Inc.

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date 8/28/2003 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EY193718341US addressed to the: Mail Stop Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Bonnie Ferguson Date Signed: 8/28/2003  
BONNIE FERGUSON

5. FEE CALCULATION (37 CFR 1.16)

CLAIMS AS FILED						
Number Filed			Number Extra		Rate	Basic Fee \$750.00
Total Claims	30	-20 =	10	X	\$18.00	180.00
Independent Claims	1	-3 =	0	X	\$84.00	0.00
Multiple dependent claim(s), if any				X	\$280.00	\$ 0.00

- [ ] Amendment cancelling extra claims enclosed.  
 [ ] Amendment deleting multiple dependencies enclosed.  
 [ ] Fee for extra claims is not being paid at this time.

Fee Calculation \$930.00

6. DECLARATION OR OATH

- [x] Enclosed  
 [ ] Not enclosed

7. FEE PAYMENT BEING MADE AT THIS TIME

[x ] basic filing fee	\$930.00
[ ] additional claims	0.00
[ ] additional independent claims	0.00
[ ] multiple dependent claims	0.00
[X] recording assignment (\$40.00)	40.00
Total Fees	\$970.00

8. METHOD OF PAYMENT OF FEES

- \_\_\_ A check in the amount of \$ \_\_\_\_\_ is enclosed.  
X Charge Account No. 01-0885 in the amount of \$ 970.00  
X A duplicate of this transmittal is attached.

9. AUTHORIZATION TO CHARGE ADDITIONAL FEES

Commissioner is hereby authorized to charge any following additional fees by this paper and during the entire pendency of this application to Account No. 01-0885.

- [ x ] 37 CFR 1.16(a), (f) or (g) (filing fees)  
 [ x ] 37 CFR 1.16(b), (c) or (d) (presentation of extra claims)

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DOCKET NO. 17609(AP)  
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of

Old et al

Serial No: Not Known

Filed: Submitted Herewith

For: CYCLOHEXYL PROSTAGLANDIN  
ANALOGS AS EP<sub>4</sub>-RECEPTOR AGONISTS

Group Art Unit: Not Known

Examiner: Not Known

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Specifically, accompanying this communication please find:

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- (e) Copies of Non-Patent References
- (f) Declaration/Power of Attorney
- (g) Assignment Cover Sheet
- (h) Assignment
- (i) New Application Transmittal
- (j) 6 sheets formal drawings
- (k) Application (45 pages)

Date:

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Respectfully submitted,

  
Bonnie Ferguson

CYCLOHEXYL PROSTAGLANDIN  
ANALOGS AS EP<sub>4</sub>-RECEPTOR AGONISTS

5

1. Field of the Invention

10 The present invention relates to cyclohexyl  
prostaglandin analogs as EP<sub>4</sub>-receptor agonists. These  
compounds are potent ocular hypotensives and are  
particularly suited for the management of glaucoma.

Background of the Invention

15

2. Description of Related Art

20 Ocular hypotensive agents are useful in the  
treatment of a number of various ocular hypertensive  
conditions, such as post-surgical and post-laser  
trabeculectomy ocular hypertensive episodes, glaucoma,  
and as presurgical adjuncts.

25 Glaucoma is a disease of the eye characterized by  
increased intraocular pressure. On the basis of its  
etiology, glaucoma has been classified as primary or  
secondary. For example, primary glaucoma in adults  
(congenital glaucoma) may be either open-angle or  
acute or chronic angle-closure. Secondary glaucoma  
results from pre-existing ocular diseases such as  
uveitis, intraocular tumor or an enlarged cataract.

30

The underlying causes of primary glaucoma are not  
yet known. The increased intraocular tension is due  
to the obstruction of aqueous humor outflow. In  
chronic open-angle glaucoma, the anterior chamber and  
its anatomic structures appear normal, but drainage of

the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

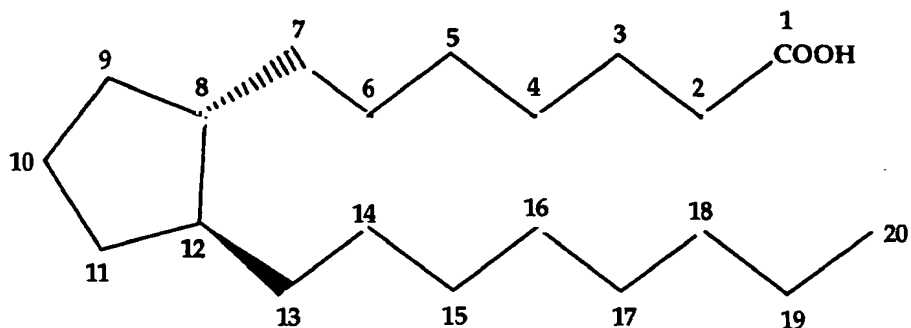
Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical  $\beta$ -adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives have been reported to possess ocular hypotensive activity, and have been recommended for use in glaucoma management. Eicosanoids and derivatives include

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numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E<sub>1</sub> (PGE<sub>1</sub>), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>)], and on the configuration of the substituents on the alicyclic ring indicated by  $\alpha$  or  $\beta$  [e.g. prostaglandin F<sub>2</sub> $\alpha$  (PGF<sub>2</sub> $\alpha$ )].

Prostaglandins were earlier regarded as potent ocular hypertensives, however, evidence accumulated in the last decade shows that some prostaglandins are highly effective ocular hypotensive agents, and are ideally suited for the long-term medical management of glaucoma (see, for example, Bito, L.Z. Biological Protection with Prostaglandins, Cohen, M.M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L.Z., Applied Pharmacology in the Medical Treatment of Glaucomas Drance, S.M. and Neufeld, A.H.

eds., New York, Grune & Stratton, 1984, pp. 477-505. Such prostaglandins include PGF<sub>2α</sub>, PGF<sub>1α</sub>, PGE<sub>2</sub>, and certain lipid-soluble esters, such as C<sub>1</sub> to C<sub>2</sub> alkyl esters, e.g. 1-isopropyl ester, of such compounds.

5        Although the precise mechanism is not yet known experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et.al., Invest. Ophthalmol. Vis. Sci. (suppl), 284 (1987)].

10        The isopropyl ester of PGF<sub>2α</sub> has been shown to have significantly greater hypotensive potency than the parent compound, presumably as a result of its more effective penetration through the cornea. In 1987, this compound was described as "the most potent  
15        ocular hypotensive agent ever reported" [see, for example, Bito, L.Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et.al., Prodrug 5 3 (1989)].

      Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface  
20        (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular PGF<sub>2α</sub> and its prodrugs, e.g., its 1-isopropyl ester, in humans. The clinical potentials of prostaglandins in the  
25        management of conditions associated with increased ocular pressure, e.g. glaucoma are greatly limited by these side effects.

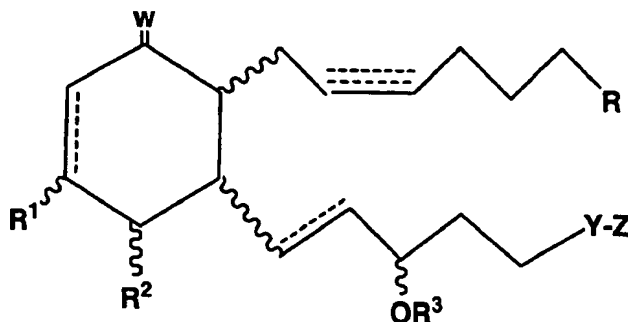
      In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin  
30        esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending USSN 596,430

(filed 10 October 1990), now U.S. Patent 5,446,041, relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl  $\text{PGF}_2\alpha$ . Intraocular pressure reducing

15 15-acyl prostaglandins are disclosed in the co-pending application USSN 175,476 (filed 29 December 1993, now abandoned). Similarly, 11,15- 9,15 and 9,11-diester of prostaglandins, for example 11,15-dipivaloyl  $\text{PGF}_2\alpha$  are known to have ocular hypotensive activity. See the  
 10 co-pending patent applications USSN Nos. 385,645 (filed 07 July 1989, now U.S. Patent 4,994,274), 584,370 (filed 18 September 1990, now U.S. Patent 5,028,624) and 585,284 (filed 18 September 1990, now U.S. Patent 5,034,413). The disclosures of all of  
 15 these patent applications are hereby expressly incorporated by reference.

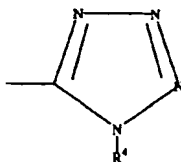
#### Summary of the Invention

The present invention concerns a method of treating ocular hypertension and/or glaucoma which  
 20 comprises administering to a mammal having ocular hypertension and/or glaucoma a therapeutically effective amount of a compound of formula I



wherein the wavy segment represents  $\alpha$  or  $\beta$  bond, a  
 25 dashed line represents the presence or absence of a

bond, R is selected from the group consisting of  $\text{CO}_2\text{R}^4$ ,  $\text{CONR}^4_2$ ,  $\text{CH}_2\text{OR}^4$ ,  $\text{CONR}^4\text{SO}_2\text{R}^4$ ,  $\text{P}(\text{O})(\text{OR}^4)$  and



wherein  $\text{R}^4$  is selected from the group consisting of H,  
 5 phenyl and lower alkyl having from one to six carbon  
 atoms and n is 0 or an integer of from 1 to 4,  $\text{R}^1$  and  
 $\text{R}^2$  are independently selected from the group consisting  
 of hydrogen, hydroxyl, a lower alkyloxy radical  
 having up to six carbon atoms, or a lower acyloxy  
 10 radical having up to six carbon atoms,  $\text{R}^3$  is selected  
 from the group consisting of hydrogen, a lower alkyl  
 radical having up to six carbon atoms and a lower acyl  
 radical having up to six carbon atoms, W is = O or  
 halogen, Y is a covalent bond or is selected from the  
 15 group consisting of  $\text{CH}_2$ , O, S and N and Z is a alkyl or  
 cycloalkyl radical including from three to ten carbon  
 atoms or an aromatic radical including a hydrocarbyl  
 aromatic radical having from six to ten carbon atoms  
 or a heterocyclic aromatic radical having from four to  
 20 ten carbon atoms and including a heterocyclic atom  
 selected from the group consisting of nitrogen, oxygen  
 and sulfur; and pharmaceutically-acceptable salts and  
 esters thereof.

In a further aspect, the present invention  
 25 relates to an ophthalmic solution comprising a  
 therapeutically effective amount of a compound of  
 formula (I), wherein the symbols have the above  
 meanings, or a pharmaceutically acceptable salt

thereof, in admixture with a non-toxic, ophthalmically acceptable liquid vehicle, packaged in a container suitable for metered application.

5 In a still further aspect, the present invention relates to a pharmaceutical product, comprising

a container adapted to dispense its contents in a metered form; and

an ophthalmic solution therein, as hereinabove defined.

10 Finally, certain of the compounds represented by the above formula, disclosed below and utilized in the method of the present invention are novel and unobvious.

15 Brief Description of the Drawing Figures

Figure 1 is a schematic of a general chemical synthesis of preparing compounds of the invention including those having an alpha chain that includes a double or triple bond.

20 Figure 2 is a schematic of the chemical synthesis of certain compounds of the invention specifically disclosed as Example 1.

25 Figure 3 is a schematic of the chemical synthesis of certain compounds of the invention specifically disclosed as Example 6.

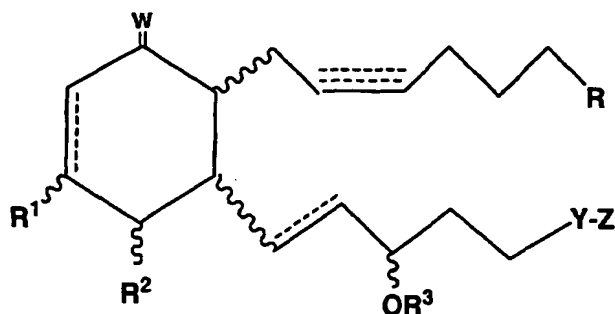
Figure 4 is a schematic of the chemical synthesis of certain compounds of the invention specifically disclosed as Example 7.

30 Figure 5 is a schematic of the chemical synthesis of certain compounds of the invention specifically disclosed as Example 9.

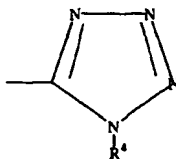
Figure 6 is a schematic of the chemical synthesis of certain compounds of the invention specifically disclosed as Example 10.

## 5 Detailed Description of the Invention

The present invention relates to the use of cyclohexyl prostaglandin analogs as EP<sub>4</sub>-receptor agonists. The compounds used in accordance with the present invention are encompassed by the following structural formula I:

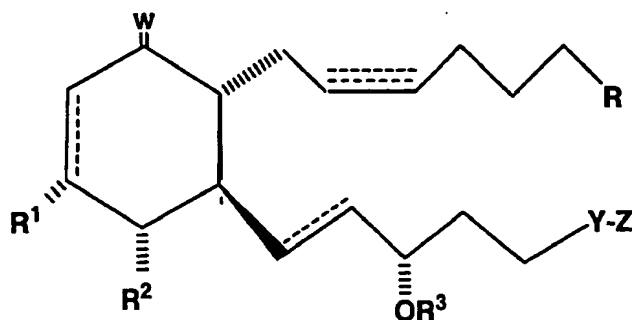


wherein the wavy segment represents  $\alpha$  or  $\beta$  bond, a dashed line represents the presence or absence of a bond, R is selected from the group consisting of CO<sub>2</sub>R<sup>4</sup>, CONR<sup>4</sup><sub>2</sub>, CH<sub>2</sub>OR<sup>4</sup>, CONR<sup>4</sup>SO<sub>2</sub>R<sup>4</sup>, P(O)(OR<sup>4</sup>) and



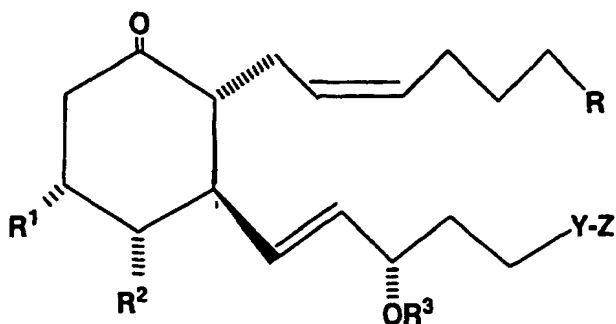
wherein R<sup>4</sup> is selected from the group consisting of H, phenyl and lower alkyl having from one to six carbon atoms and n is 0 or an integer of from 1 to 4. R<sup>1</sup> and

A preferred group of the compounds of the present invention includes compounds that have the following structural formula II:



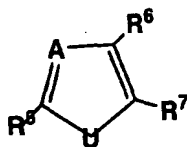
wherein the hatched segment represents an  $\alpha$  bond and the solid triangle represents a  $\beta$  bond.

Another preferred group includes compounds having the formula III:



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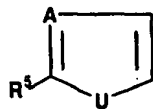
The most preferred group of compounds utilized in the method of the present invention are selected from the group wherein Z is phenyl or represented by the formula IV



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wherein U is selected from the group consisting of O and S, A is selected from the group consisting of N, -CH and C, R<sup>5</sup> is selected from the group consisting of hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms and lower alkoxy having from 1 to 6 carbon atoms, R<sup>6</sup> and R<sup>7</sup> are selected from the group consisting of hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms and lower alkoxy having from 1 to 6 carbon atoms, or, together with

20



, R<sup>6</sup> and R<sup>7</sup> forms a condensed aryl ring.

Preferably R is CO<sub>2</sub>R<sup>4</sup> and more preferably R<sup>4</sup> is H or methyl.

5        The above compounds of the present invention may be prepared by methods that are known in the art or according to the working examples below. The compounds, below, are especially preferred representative of the compounds of the present invention.

10

(Z)-7-((1R,2R)-2-[(E)-5-(3-Chloro-benzo[b]thiophen-2-yl)-3-hydroxy-pent-1-enyl]-6-oxo-cyclohexyl)-hept-5-enoic acid

15

(Z)-7-((1R,6R)-6-[(E)-5-(3-Chloro-benzo[b]thiophen-2-yl)-3-hydroxy-pent-1-enyl]-2-oxo-cyclohex-3-enyl)-hept-5-enoic acid

20

7-[(1R,2R,3R)-3-Hydroxy-2-((S)-3-hydroxy-octyl)-6-oxo-cyclohexyl]-heptanoic acid

7-[(1R,2R,3R)-3-Hydroxy-2-((E)-3-hydroxy-5-phenyl-pent-1-enyl)-6-oxo-cyclohexyl]-hept-5-ynoic acid

25

(Z)-7-((1R,2R,3R)-2-[(E)-5-(3-Chloro-benzo[b]thiophen-2-yl)-3-hydroxy-pent-1-enyl]-3-hydroxy-6-oxo-cyclohexyl)-hept-5-enoic acid

(Z)-7-[(1R,2R,3R)-3-Hydroxy-2-((E)-3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-cyclohexyl]-hept-5-enoic acid

5 7-[(1R,2R,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxy-but-1-enyl)-3-hydroxy-6-oxo-cyclohexyl]-hept-5-ynoic acid

10 (Z)-7-[(1R,2R,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxy-but-1-enyl)-3-hydroxy-6-oxo-cyclohexyl]-hept-5-enoic acid

15 (Z)-7-[(1R,2R,4S)-4-Hydroxy-2-((E)-3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-cyclohexyl]-hept-5-enoic acid

20 (Z)-7-[(1R,2R,3R,6R)-6-Chloro-2-[(E)-5-(3-chloro-benzo[b]thiophen-2-yl)-3-hydroxy-pent-1-enyl]-3-hydroxy-cyclohexyl]-hept-5-enoic acid

25 A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Of particular interest are salts formed with inorganic ions, such as sodium, potassium, calcium, magnesium and zinc.

30 Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable acid addition salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients,

and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 6.5 and 7.2 with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate

buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

	<u>Ingredient</u>	<u>Amount (% w/v)</u>
	active ingredient	about 0.001-5
	preservative	0-0.10
20	vehicle	0-40
	tonicity adjustor	1-10
	buffer	0.01-10
	pH adjustor	q.s. pH 4.5-7.5
	antioxidant	as needed
25	surfactant	as needed
	purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers

equipped with a dropper, to facilitate the application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between  
5 about 0.5 and about 15 ml solution.

The invention is further illustrated by the following non-limiting Examples, which are summarized in the reaction schemes of Figures 1 and 2, wherein the compounds are identified by the same designator in  
10 both the Examples and the Figures.

#### EXAMPLE 1

(Z)-7-[(1R,2R,3R)-2-[(E)-5-(3-Chloro-benzo[b]thiophen-  
15 2-yl)-3-hydroxy-pent-1-enyl]-3-hydroxy-6-oxo-cyclohexyl]-hept-5-enoic acid (7H and 7L, Figure 2)

Step 1. Three component coupling of 1a, 2a and 3 to give 4.

20 tert-Butyl lithium (1.7 M in pentane, 1.93 mL, 3.3 mmol) was added to a solution of {(E)-1-[2-(3-chloro-benzo[b]thiophen-2-yl)-ethyl]-3-iodo-allyloxy}-tert-butyltrimethylsilane (2a, 740 mg, 1.5 mmol) in THF (3.0 mL) at -78 °C under nitrogen. (2a was prepared  
25 as disclosed in U.S. Patent Application Serial No. 365,369 which was filed on February 11, 2003 and is hereby incorporated by reference.) After 15 min at -78 °C, dimethylzinc (2.0 M in PhMe, 0.73 mL, 1.5 mmol) was added and the reaction solution was warmed to 0  
30 °C. After 15 min at 0 °C. the reaction was recooled to -78 °C. A solution of enone 1a (226 mg, 1.0 mmol) in THF (1.0 mL) was added over 50 min via syringe

pump, rinsing the syringe with THF (0.5 mL). 1a was prepared as disclosed in (López-Pelegrín, J. A.; Janda, K. D. *Chem. Eur. J.* 2000, 6, 1917-1922 and references therein.) After 15 min, HMPA (1.74 mL, 10.0 mmol) was added. After an additional 15 min, a solution of propargyl iodide 3 (1.33 g, 5.0 mmol) in THF (3.0 mL) was added. (3 was prepared from the corresponding propargylic alcohol [Casy, G.; Petersen, J. W.; Taylor, R. J. K. *Org. Synth.* 1993, Collect. Vol. VIII, 415-420] using iodine, triphenylphosphine and imidazole in dichloromethane solvent.)

The reaction was then placed into a cryobath at -40°C and maintained at that temperature for 21 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (40 mL) and extracted with EtOAc (3x25 mL). The combined organic phases were washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. Purification of the resulting residue by flash column chromatography on silica gel (0 → 7% EtOAc/Hex, gradient) afforded 335 mg (46%) of desired product 4.

Step 2. Deprotection to give 5H and 5L.

HF-pyridine (0.6 mL) was added to a solution of the bis-silyl ether from step 1 (4, 150 mg, 0.21 mmol) in MeCN (4.0 mL) in a plastic scintillation vial. After stirring overnight at rt, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  (20 mL) and extracted with EtOAc (3x25 mL). The organic phase was washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. Purification of the resulting

(50 → 100% EtOAc/Hex, gradient) afforded 29.2 mg (28%) of the high Rf diastereomer (5H) and 26.5 mg (26%) of the low Rf diastereomer (5L).

5      Step 3.    Reduction of alkyne to give alkene 6H and 6L.

          Method A.    Pd/C (10 mol%, 2 mg) was added to a solution of the high Rf alkyne from step 2 (5H, 6.0 mg, 0.012 mmol) in MeOH (1.5 mL).    A hydrogen  
10    atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 1.25 h.    The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo.    Purification of  
15    the resulting residue by preparative thin layer chromatography (silica, 100% EtOAc) afforded 4.6 mg (76%) of 6H with 1.0 mg of recovered 5H.

          Method B.    Lindlar catalyst (20 mg) was added to a solution of the low Rf alkyne from step 2 (5L, 20  
20    mg, 0.04 mmol) in EtOAc (2.0 mL).    A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 19 h.    The reaction mixture was filtered through celite,  
25    washing with EtOAc, and the filtrate was concentrated in vacuo.    Purification of the resulting residue by preparative thin layer chromatography (silica, 100% EtOAc) afforded 4.8 mg (24%) of 6L along with 10 mg of recovered 5L.

30

          Step 4.    Conversion of ester to acid 7H and 7L.

Method A. A solution of the ester from step 3A (6H, 2.6 mg, 0.005 mmol), MeCN (0.1 mL), pH 7.2 phosphate buffer (2.0 mL) and pig liver esterase (50  $\mu$ L) were stirred together overnight at rt. The mixture was extracted with EtOAc (2x10 mL). The combined extracts were washed with brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo to afford 2.0 mg (79%) of the title compound (7H).

Method B. A solution of the ester from step 3B (6L, 3 mg, 0.006 mmol), MeCN (0.1 mL), pH 7.2 phosphate buffer (3.0 mL) and rabbit liver esterase (1 mg) were stirred together overnight at rt. The mixture was concentrated in vacuo to dryness. Purification of the resulting residue by preparative thin layer chromatography (silica, 10% MeOH/ $\text{CH}_2\text{Cl}_2$ ) afforded 0.8 mg (27%) of the title compound (7L).

## EXAMPLE 2

(Z)-7-[(1R,2R,3R)-3-Hydroxy-2-((E)-3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-cyclohexyl]-hept-5-enoic acid

Prepared from ((E)-1-Benzyl-3-iodo-allyloxy)-tert-butyldimethylsilane (2b) and enone 1a in accordance with the procedures in Example 1 (steps 1, 2, 3B and 4B). (2b was prepared analogously to 2a, above.)

## EXAMPLE 3

(Z)-7-[(1R,2R,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-hydroxy-but-1-enyl)-3-hydroxy-6-oxo-cyclohexyl]-hept-5-enoic acid

Prepared from ((E)-1-Benzo[b]thiophen-3-ylmethyl-3-iodo-allyloxy)-tert-butyldimethylsilane (2c) and enone 1a in accordance with the procedures in Example 1 (steps 1, 2 and 4B) and 3C (see below). (2c was prepared analogously to 2a, above.)

Step 3. Reduction of alkyne to give alkene.

Method C. Sodium borohydride (8.0 mg, 0.21 mmol) was added to a suspension of nickel (II) chloride (55 mg, 0.43 mmol) in 95% ethanol (2.0 mL) and the mixture immediately turned black. After 5 min at rt, ethylenediamine (46  $\mu$ L, 0.69 mmol) was added. After 15 min at rt, the alkyne from step 2 (40 mg, 0.085 mmol) was added in 95% ethanol (2.0 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen for 19 h. The reaction mixture was filtered through celite, washing with ethanol, and the filtrate was concentrated in vacuo. Purification of the resulting residue by flash column chromatography (50  $\rightarrow$  100% EtOAc/Hex, gradient) afforded 20 mg (50%) of the desired alkene.

#### EXAMPLE 4

7-[(1R,2R,3R)-3-Hydroxy-2-((E)-3-hydroxy-5-phenylpent-1-enyl)-6-oxo-cyclohexyl]-hept-5-ynoic acid

Prepared from ((E)-3-iodo-1-phenethyl-allyloxy)-tert-butyldimethylsilane (2d) and enone 1a in accordance with the procedures in Example 1 (steps 1,

2 and 4B). (2d was prepared analogously to 2a, above.)

#### EXAMPLE 5

5

(Z)-7-[(1R,2R,4S)-4-Hydroxy-2-((E)-3-hydroxy-4-phenyl-but-1-enyl)-6-oxo-cyclohexyl]-hept-5-enoic acid

Prepared from (2b) and (S)-5-(tert-butyltrimethylsiloxy)-2-cyclohexenone (1b) in accordance with the procedures in Examples 1 and 3 (steps 1, 2, 3C and 4B). (1b was prepared as described in Hareau, G. P-J. et. al.; J. Am. Chem. Soc. 1999, 121, 3640-50.)

15

#### EXAMPLE 6

(Z)-7-[(1R,2R,3R,6R)-6-Chloro-2-[(E)-5-(3-chlorobenzo[b]thiophen-2-yl)-3-hydroxy-pent-1-enyl]-3-hydroxy-cyclohexyl]-hept-5-enoic acid (11L, Figure 3)

20

Step 1. Conversion of ketone 4 to  $\alpha$ -alcohol 8.

L-selectride (1.0 M in THF, 0.76 mL, 0.76 mmol) was added to a solution of the product of Example 1, step 1 (4, 370 mg, 0.51 mmol) in THF (5.0 mL) at -78 °C under nitrogen. After 30 min, formic acid (0.4 mL) was added and the reaction was allowed to warm to 0 °C. After 30 min, aqueous HCl (1.0 M, 5 mL) was added and the mixture was extracted with EtOAc (3x30 mL). The combined organic phase was washed with brine then dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. Purification of the resulting residue by flash column

30

chromatography on silica gel (10 → 15% EtOAc/Hex, gradient) afforded 194 mg (53%) of 8.

Step 2. Conversion of alcohol 8 to mesylate 9.

5       Methanesulfonyl chloride (24  $\mu$ L, 0.31 mmol) and triethylamine (54  $\mu$ L, 0.39 mmol) were added sequentially to a solution of the alcohol from step 1 (8, 188 mg, 0.26 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) at rt. After 5 h, an additional portion of methanesulfonyl chloride 10 (40  $\mu$ L, 0.51 mmol) and triethylamine (54  $\mu$ L, 0.39 mmol) were added. After stirring overnight at rt, saturated aqueous  $\text{NaHCO}_3$  (10 mL) was added and the reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3x15 mL). The combined organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. Purification of the 15 resulting residue by flash column chromatography on silica gel (10 → 20% EtOAc/Hex, gradient) afforded 134 mg (64%) of 9.

20       Step 3. Conversion of  $\alpha$ -mesylate 9 to  $\beta$ -chloride 10.

      The mesylate from step 2 (9, 130 mg, 0.16 mmol), tetrabutylammonium chloride (445 mg, 1.6 mmol) and toluene (5.0 mL) were combined and stirred together at 40  $^\circ\text{C}$  under nitrogen overnight. The reaction was 25 cooled to rt, brine (10 mL) was added, and the mixture was extracted with EtOAc (3x15 mL). The combined organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. Purification of the resulting residue by flash column chromatography on silica gel 30 (10% EtOAc/Hex) afforded 31 mg (26%) of 10 along with 53 mg of recovered 9.

The product of step 3 was then converted to the title product (11) in accordance with the procedures in Examples 1 and 3 (steps 2, 3C and 4B).

5      EXAMPLE 7

(Z)-7-((1R,2R)-2-[(E)-5-(3-Chloro-benzo[b]thiophen-2-yl)-3-hydroxy-pent-1-enyl]-6-oxo-cyclohexyl)-hept-5-enoic acid (15L, Figure 4).

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Step 1. Three component coupling of 1b, 2a and 3 to give 12.

The three component coupling product 12 was obtained from vinyl iodide 2a and enone 1b in accordance with the procedure in Example 1 (step 1).

15

Step 2. Deprotection and elimination to give 13H and 13L.

A mixture of the  $\beta$ -silyloxy ketone (12, 198 mg, 0.27 mmol) and acetic acid/THF/H<sub>2</sub>O (2:1:1, 2.0 mL) was heated at 70 °C overnight. The reaction was cooled to rt, saturated aqueous NaHCO<sub>3</sub> (20 mL) was added and the mixture was extracted with EtOAc (2x20 mL). The combined organic phase was washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. <sup>1</sup>H NMR analysis showed that the elimination reaction was incomplete, so the crude material was resubmitted to the reaction conditions for 3 d. The reaction was cooled to rt, saturated aqueous NaHCO<sub>3</sub> (15 mL) was added and the mixture was extracted with EtOAc (3x10 mL). The combined organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. Purification of the resulting residue by preparative thin layer

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chromatography (silica, 50% EtOAc/Hex) afforded 7.4 mg (6%) of 13H and 3.7 mg (3%) of 13L.

Step 3. Reduction to give 14L.

5           Pd/C (10 mol%, 1 mg) was added to a solution of  
the low Rf diastereomer from step 2 (13L, 3.7 mg,  
0.0076 mmol) in MeOH (1.0 mL). A hydrogen atmosphere  
was established by evacuating and refilling with  
hydrogen (3x) and the reaction mixture was stirred  
10 under a balloon of hydrogen for 1 h. The reaction  
mixture was filtered through celite and the filtrate  
was concentrated in vacuo. Purification of the  
resulting residue by preparative thin layer  
chromatography (silica, 30% EtOAc/Hex) afforded 2.3  
15 mg (61%) of 14L.

The product of step 3 was then converted to the  
title product 15L in accordance with the procedure in  
Example 1 (step 4B).

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#### EXAMPLE 8

7-[(1R,2R,3R)-2-((E)-4-Benzo[b]thiophen-3-yl-3-  
hydroxy-but-1-enyl)-3-hydroxy-6-oxo-cyclohexyl]-hept-  
25 5-ynoic acid

Prepared from vinyl iodide 2c and enone 1a in  
accordance with the procedures in Example 1 (steps 1,  
2 and 4B).

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## EXAMPLE 9

7-[(1R,2R,3R)-3-Hydroxy-2-((S)-3-hydroxy-octyl)-6-oxo-cyclohexyl]-heptanoic acid (20, Figure 5).

5

Step 1. Three component coupling to give 17 via enoxysilane 16.

A solution of [(S)-1-((E)-2-iodo-vinyl)-hexyloxy]-tert-butyldimethylsilane (2e, 500 mg, 1.36 mmol) in Et<sub>2</sub>O (7.0 mL) at -78 °C under nitrogen was treated with tert-butyl lithium (1.7 M in pentane, 1.6 mL, 2.72 mmol). (2e was purchased from Nissan Chemical Industries.) After 30 min at -78°C, lithium 2-thienylcyanocuprate (0.25 M in THF, 5.44 mL, 1.36 mmol) was added. After 30 min at -78°C, a solution of enone 1a (237 mg, 1.05 mmol) in Et<sub>2</sub>O (1.0 mL) was added dropwise. After 1.5 h min at -78°C, TMSCl (0.80 mL, 6.3 mmol) was added. After 15 min at -78°C, Et<sub>3</sub>N (1.9 mL, 13.6 mmol) was added and the solution was allowed to warm to rt. The mixture was poured into hexanes and water. The phases were separated and the aqueous phase was extracted with additional hexanes (3x50 mL). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. A solution of crude enoxysilane 16 (~1.0 mmol) in THF (6.0 mL) at -23°C under nitrogen was treated with methyl lithium (1.4 M in Et<sub>2</sub>O, 1.1 mL, 1.5 mmol). After 30 min, the solution was cooled to -78°C then a solution of iodide 3 (1.06 g, 4.0 mmol) in THF (7.0 mL) was added via cannula. After 1 h at -78°C, the reaction was warmed to -23°C for 2 h then allowed to

warm to rt. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (50 mL) and extracted with EtOAc (3x30 mL). The combined organic phases were washed with brine (75 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. Purification of the resulting residue by flash column chromatography on silica gel (0  $\rightarrow$  10% EtOAc/Hex) afforded 157 mg (25%) of 17.

Step 2. Deprotection to give 18.

HF-pyridine (0.3 mL) was added to a solution of the bis-silyl ether from step 1 (17, 150 mg, 0.25 mmol) in MeCN (3.0 mL) in a plastic scintillation vial. After stirring overnight at rt, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  (20 mL) and extracted with EtOAc (2x25 mL). The organic phase was washed with brine (25 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. Purification of the resulting residue by flash column chromatography on silica gel (40  $\rightarrow$  80% EtOAc/Hex, gradient) afforded 61 mg (65%) of 18.

Step 3. Reduction of the alkyne and the alkene to give 19.

$\text{Pd/C}$  (10 mol%, 5 mg) was added to a solution of the product from step 2 (18, 15 mg, 0.039 mmol) in MeOH (1.5 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and the reaction mixture was stirred under a balloon of hydrogen overnight. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. Purification of the resulting

residue by flash column chromatography (30% → 50% EtOAc/Hex, gradient) afforded 3.7 mg (25%) of 19.

Step 4. Conversion of ester to acid 20.

5           The product of step 3 was converted to the title product (20) in accordance with the procedure in Example 1 (step 4B).

#### EXAMPLE 10

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(Z)-7-((1R,6R)-6-[(E)-5-(3-Chloro-benzo[b]thiophen-2-yl)-3-hydroxy-pent-1-enyl]-2-oxo-cyclohex-3-enyl)-hept-5-enoic acid (24L, Figure 6)

15       Step 1. Deprotection to give 21H and 21L.

          HF-pyridine (1.5 mL) was added to a solution of the bis-silyl ether from Example 7, step 1 (12, 421 mg, 0.58 mmol) in MeCN (5.0 mL) in a plastic scintillation vial. After stirring 3 h at rt, the reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (25 mL) and extracted with EtOAc (3x25 mL). The organic phase was washed with brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. Purification of the resulting residue by preparative thin layer chromatography (silica, 70% EtOAc/Hex) afforded 37 mg (13%) of 21H and 22 mg (8%) of 21L.

Step 2. Reduction of alkyne to alkene 22L.

30           Pd/C (10 mol%, 2 mg) was added to a solution of the product from step 1 (21L, 13 mg, 0.026 mmol) in MeOH (1.0 mL). A hydrogen atmosphere was established by evacuating and refilling with hydrogen (3x) and

the reaction mixture was stirred under a balloon of hydrogen for 4.5 h. The reaction mixture was filtered through celite, washing with MeOH, and the filtrate was concentrated in vacuo. Purification of the resulting residue by preparative thin layer chromatography (silica, 90% EtOAc/Hex) afforded 7.5 mg (57%) of 22L.

Step 3. Elimination of  $\beta$ -hydroxy ketone to enone 23L.

A mixture of the product from step 2 (22L, 7.5 mg, 0.015 mmol) and acetic acid/THF/H<sub>2</sub>O (2:1:1, 1.0 mL) was heated at 70 °C overnight. The reaction was cooled to rt, saturated aqueous NaHCO<sub>3</sub> (7 mL) was added and the mixture was extracted with EtOAc (2x6 mL). The combined organic phase was washed with brine (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. Purification of the resulting residue by preparative thin layer chromatography (silica, 50% EtOAc/Hex) afforded 5.0 mg (69%) of 23L.

Step 4. Conversion of ester to acid 24L

The product of step 3 was then converted to the title product (24L) in accordance with the procedure in Example 1 (step 4B).

#### HUMAN RECOMBINANT EP<sub>4</sub> RECEPTOR: STABLE TRANSFECTANTS.

Plasmids encoding the human EP<sub>4</sub> receptor were prepared by cloning the respective coding sequences into the eukaryotic expression vector pCEP4

(Invitrogen). The pCEP4 vector contains an Epstein Barr virus (EBV) origin of replication, which permits episomal replication in primate cell lines expressing EBV nuclear antigen (EBNA-1). It also contains a hygromycin resistance gene that is used for eukaryotic selection. The cells employed for stable transfection were human embryonic kidney cells (HEK-293) that were transfected with and express the EBNA-1 protein. These HEK-293-EBNA cells (Invitrogen) were grown in medium containing Geneticin (G418) to maintain expression of the EBNA-1 protein. HEK-293 cells were grown in DMEM with 10% fetal bovine serum (FBS), 250  $\mu\text{g ml}^{-1}$  G418 (Life Technologies) and 200  $\mu\text{g ml}^{-1}$  gentamicin or penicillin/streptomycin. Selection of stable transfectants was achieved with 200  $\mu\text{g ml}^{-1}$  hygromycin, the optimal concentration being determined by previous hygromycin kill curve studies.

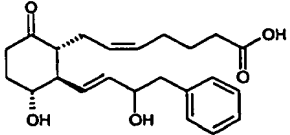
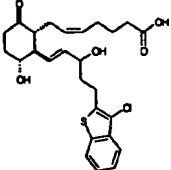
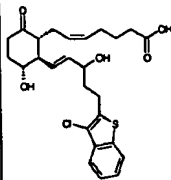
For transfection, the cells were grown to 50-60% confluency on 10 cm plates. The plasmid pCEP4 incorporating cDNA inserts for the respective human prostanoid receptor (20  $\mu\text{g}$ ) was added to 500  $\mu\text{l}$  of 250 mM  $\text{CaCl}_2$ . HEPES buffered saline x 2 (2 x HBS, 280 mM NaCl, 20 mM HEPES acid, 1.5 mM  $\text{Na}_2\text{HPO}_4$ , pH 7.05 - 7.12) was then added dropwise to a total of 500  $\mu\text{l}$ , with continuous vortexing at room temperature. After 30 min, 9 ml DMEM were added to the mixture. The DNA/DMEM/calcium phosphate mixture was then added to the cells, which had been previously rinsed with 10 ml PBS. The cells were then incubated for 5 hr at 37° C in humidified 95% air/5%  $\text{CO}_2$ . The calcium phosphate solution was then removed and the cells were treated with 10% glycerol in DMEM for 2 min. The glycerol solution was then replaced by DMEM with

10% FBS. The cells were incubated overnight and the medium was replaced by DMEM/10% FBS containing 250  $\mu\text{g ml}^{-1}$  G418 and penicillin/streptomycin. The following day hygromycin B was added to a final concentration of 200  $\mu\text{g ml}^{-1}$ .

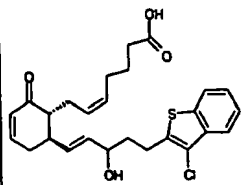
Ten days after transfection, hygromycin B resistant clones were individually selected and transferred to a separate well on a 24 well plate. At confluence each clone was transferred to one well of a 6 well plate, and then expanded in a 10 cm dish. Cells were maintained under continuous hygromycin selection until use.

Certain of the above compounds were tested for activity in the recombinant human EP<sub>4</sub> receptor assay described above and the results are reported in Table 1, below.

TABLE 1

Example #	Structure	Comment	Binding Data (IC <sub>50</sub> in nM)	Functional Data (EC <sub>50</sub> in nM)
			hEP4	hEP4
2		low Rf	100	11
1		low Rf	400	67
1		high Rf	200	136

3		low Rf	1300	168
4		low Rf	1000	214
5		low Rf	500	251
6		low Rf	35	314
7		low Rf	1500	358
8		high Rf	3500	362
9			600	387

10		low RF	1800	456
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EP activity indicates that the compounds of this invention are useful in treating asthma, dysmenorrhea as well as glaucoma and lowering intraocular pressure.

5 Other potential therapeutic applications are in osteoporosis, constipation, renal disorders, sexual dysfunction, baldness and in disorder of immune regulation.

10 EP receptor agonists may be useful for prevention and/or treatment of the following diseases:

acute hepatitis, asthma, bronchitis, burn, chronic obstructive respiratory diseases, Crohn's disease,  
 15 digestive ulcer, glaucoma (and other diseases related to elevated intraocular pressure), hemophagous syndrome, hepatopathy, hypercytokinemia at dialysis, hypertension, immunological diseases (autoimmune diseases, organ transplantation, etc.), inflammation  
 20 (such as rheumatoid arthritis), Kawasaki disease, liver injury, macrophage activation syndrome, myocardial ischemia, nephritis, nerve cell death, osteoporosis and diseases associated with bone disorders, premature birth, pulmonary emphysema,  
 25 pulmonary fibrosis, pulmonary injury, renal failure, sepsis, sexual dysfunction, shock, sleep disorder, Still disease, stomatitis, systemic granuloma,

systemic inflammatory syndrome, thrombosis and stroke, ulcerative colitis.

5       The compounds of the invention may also be useful in the treatment of various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris, in which case the compounds may be administered by any means that effect  
10       vasodilation and thereby relieve the symptoms of the disease. For example, administration may be by oral, transdermal, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes.

15       The compounds of the invention may be formulated into an ointment containing about 0.10 to 10% of the active ingredient in a suitable base of, for example, white petrolatum, mineral oil and petrolatum and lanolin alcohol. Other suitable bases  
20       will be readily apparent to those skilled in the art.

      The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional dissolving or suspending the compounds, which are all  
25       either water soluble or suspendable. For administration in the treatment of the other mentioned pathophysiological disorders. The pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as  
30       soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in liquid form that may be mixed with fillers such as

lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as in buffered salt solution. In addition, stabilizers may be added.

In addition to being provided in a liquid form, for example in gelatin capsule or other suitable vehicle, the pharmaceutical preparations may contain suitable excipients to facilitate the processing of the active compounds into preparations that can be used pharmaceutically. Thus, pharmaceutical preparations for oral use can be obtained by adhering the solution of the active compounds to a solid support, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch, paste using for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, crosslinked polyvinyl pyrrolidone, agar, or algenic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all,

flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with  
5 suitable coatings which if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and  
10 suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used.  
15 Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

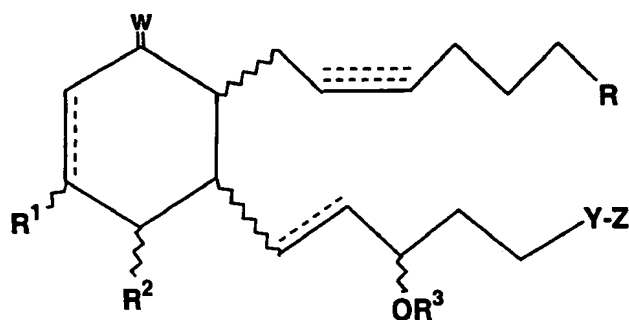
Suitable formulations for intravenous or  
20 parenteral administration include aqueous solutions of the active compounds. In addition, suspensions of the active compounds as oily injection suspensions may be administered. Aqueous injection suspensions may contain substances which increase the viscosity of the  
25 suspension include, for example, sodium carboxymethyl cellulose, soribitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The foregoing description details specific methods and compositions that can be employed to  
30 practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties

can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.

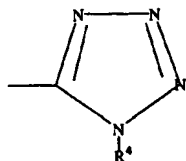
## CLAIMS

1. A method of treating ocular hypertension or  
 5 glaucoma which comprises administering to a mammal  
 having ocular hypertension or glaucoma a  
 therapeutically effective amount of a compound  
 represented by formula I:



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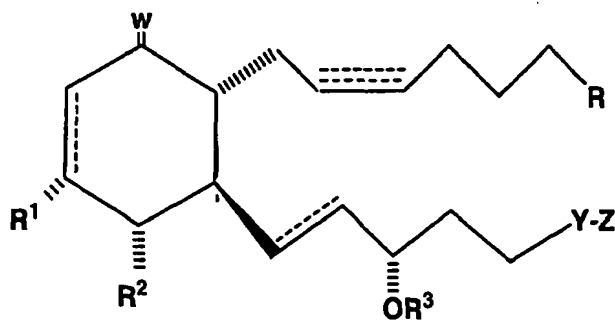
- wherein the wavy segment represents an  $\alpha$  or  $\beta$  bond, a  
 dashed line represents the presence or absence of a  
 bond, R is selected from the group consisting of  $\text{CO}_2\text{R}^4$ ,  
 15  $\text{CONR}^4_2$ ,  $\text{CH}_2\text{OR}^4$ ,  $\text{CONR}^4\text{SO}_2\text{R}^4$ ,  $\text{P}(\text{O})(\text{OR}^4)$  and



- wherein  $\text{R}^4$  is selected from the group consisting of H,  
 phenyl and lower alkyl having from one to six carbon  
 atoms and n is 0 or an integer of from 1 to 4,  $\text{R}^1$  and  
 20  $\text{R}^2$  are independently selected from the group consisting  
 of hydrogen, hydroxyl, a lower alkyloxy radical

having up to six carbon atoms, or a lower acyloxy radical having up to six carbon atoms,  $R^3$  is selected from the group consisting of hydrogen, a lower alkyl radical having up to six carbon atoms and a lower acyl radical having up to six carbon atoms, W is = O or halogen, Y is a covalent bond or is selected from the group consisting of  $CH_2$ , O, S and N and Z is a alkyl or cycloalkyl radical including from three to ten carbon atoms or an aromatic radical including a hydrocarbyl aromatic radical having from six to ten carbon atoms or a heterocyclic aromatic radical having from four to ten carbon atoms and including a heterocyclic atom selected from the group consisting of nitrogen, oxygen and sulfur; and pharmaceutically-acceptable salts and esters thereof.

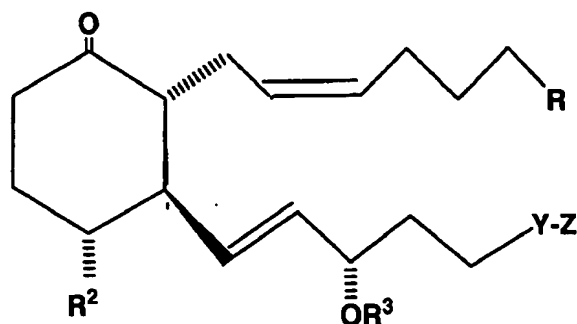
2. The method of Claim 1 wherein said compound is represented by formula II:



wherein the hatched segment represents an  $\alpha$  bond and the solid triangle represents a  $\beta$  bond.

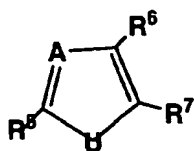
3. The method of claim 2 wherein said compound is represented by formula III

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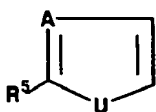
4. The method of claim 3 wherein Z is phenyl or is represented by the formula IV

10



wherein U is selected from the group consisting of O  
 15 and S, A is selected from the group consisting of N,  
 -CH, and C, R⁵ is selected from the group consisting  
 of hydrogen, halogen, lower alkyl having from 1 to 6  
 carbon atoms, and lower alkoxy having from 1 to 6  
 carbon atoms, R⁶ and R⁷ are selected from the group  
 20 consisting of hydrogen, halogen, lower alkyl having

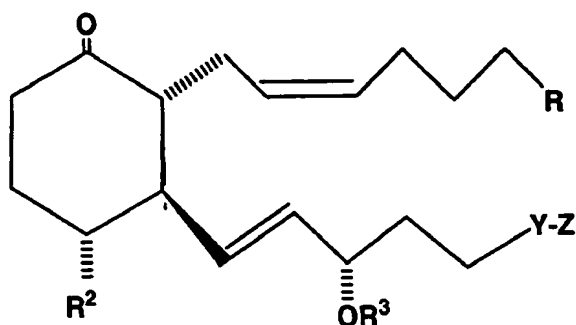
from 1 to 6 carbon atoms, lower alkoxy having from 1 to 6 carbon atoms or, together with



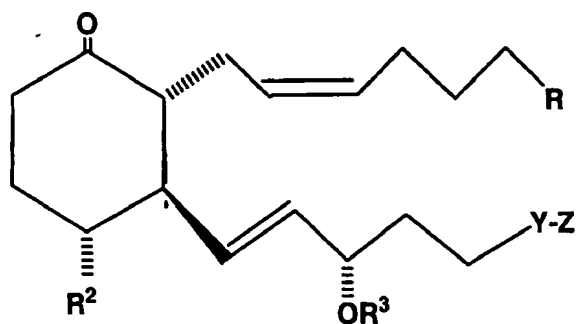
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,  $R^6$  and  $R^7$  forms a condensed aryl ring.

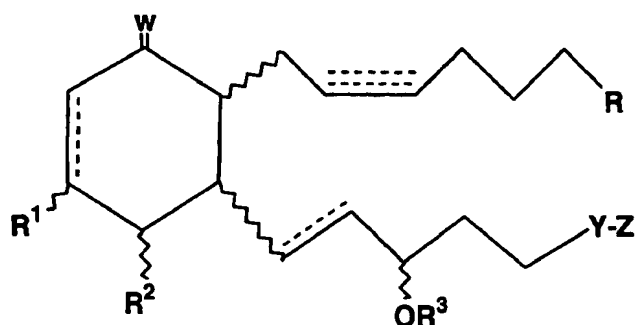
5. The method of claim 4 wherein U is S.
6. The method of claim 4 wherein R is  $\text{CO}_2\text{R}^4$ .
- 10 7. The method of claim 6 wherein R is H or methyl.
8. The method of claim 4 wherein Z is phenyl.
9. The method of claim 8 wherein R is  $\text{CO}^2\text{R}_4$ .
10. The method of claim 9 wherein  $\text{R}^4$  is H.
11. The method of claim 4 wherein Z is
- 15 chlorobenzothienyl.
12. The method of claim 11 wherein R is  $\text{CO}^2\text{R}_4$ .
13. The method of claim 12 wherein  $\text{R}^4$  is H.
14. An ophthalmic solution comprising a
- therapeutically effective amount of a compound of
- 20 formula I, as defined in Claim 1, or a
- pharmaceutically acceptable salt thereof, in admixture
- with a non-toxic, ophthalmically acceptable liquid
- vehicle, packaged in a container suitable for metered
- application.
- 25 15. The ophthalmic solution of Claim 14 wherein said
- compound is a compound of Formula III



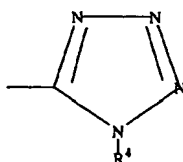
16. A pharmaceutical product, comprising a container adapted to dispense the contents of said container in metered form; and an ophthalmic solution in said container comprising a compound of formula I as defined in Claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a non-toxic, ophthalmically acceptable liquid vehicle.
17. The product of claim 16 wherein said compound is compound of Formula III



18. The product of claim 17 wherein Z is phenyl.
19. The product of claim 18 wherein R is CO<sub>2</sub>R<sup>4</sup> wherein R<sup>4</sup> is H or methyl.
20. The product of claim 19 wherein R<sup>4</sup> is H.
21. The compound represented by formula I:



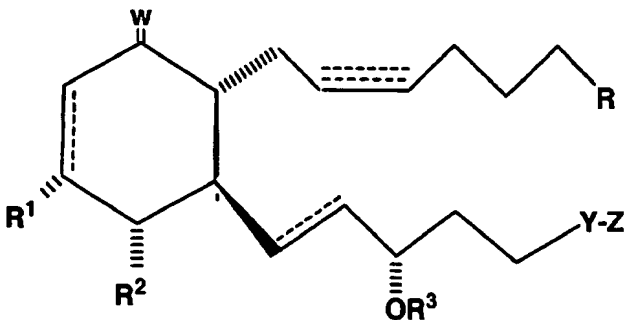
wherein the wavy segment represents an  $\alpha$  or  $\beta$  bond, a  
 dashed line represents the presence or absence of a  
 5 bond, R is selected from the group consisting of  $\text{CO}_2\text{R}^4$ ,  
 $\text{CONR}^4_2$ ,  $\text{CH}_2\text{OR}^4$ ,  $\text{CONR}^4\text{SO}_2\text{R}^4$ ,  $\text{P}(\text{O})(\text{OR}^4)$  and



10 wherein  $\text{R}^4$  is selected from the group consisting of H,  
 phenyl and lower alkyl having from one to six carbon  
 atoms and n is 0 or an integer of from 1 to 4,  $\text{R}^1$  and  
 $\text{R}^2$  are independently selected from the group consisting  
 of hydrogen, hydroxyl, a lower alkyloxy radical  
 15 having up to six carbon atoms, or a lower acyloxy  
 radical having up to six carbon atoms,  $\text{R}^3$  is selected  
 from the group consisting of hydrogen, a lower alkyl  
 radical having up to six carbon atoms and a lower acyl  
 radical having up to six carbon atoms, W is = O or  
 20 halogen, Y is a covalent bond or is selected from the  
 group consisting of  $\text{CH}_2$ , O, S and N and Z is a alkyl or

cycloalkyl radical including from three to ten carbon atoms or an aromatic radical including a hydrocarbyl aromatic radical having from six to ten carbon atoms or a heterocyclic aromatic radical having from four to ten carbon atoms and including a heterocyclic atom selected from the group consisting of nitrogen, oxygen and sulfur; and pharmaceutically-acceptable salts and esters thereof.

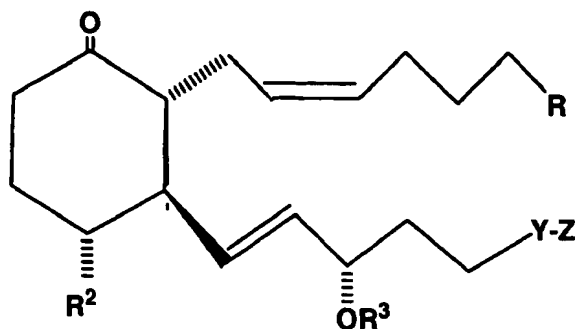
22. The compound of claim 1 wherein said compound is represented by formula II:



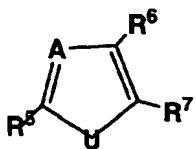
- wherein the hatched segment represents an  $\alpha$  bond and the solid triangle represents a  $\beta$  bond.

23. The method of claim 22 wherein said compound is represented by formula III

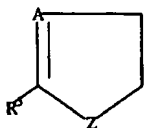
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24. The method of claim 23 wherein Z is phenyl or is represented by the formula IV



- 5 wherein Z is selected from the group consisting of O and S, A is selected from the group consisting of N, -CH, and C, R<sup>5</sup> is selected from the group consisting of hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, and lower alkoxy having from 1 to 6
- 10 carbon atoms, R<sup>6</sup> and R<sup>7</sup> are selected from the group consisting of hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, lower alkoxy having from 1 to 6 carbon atoms or, together with



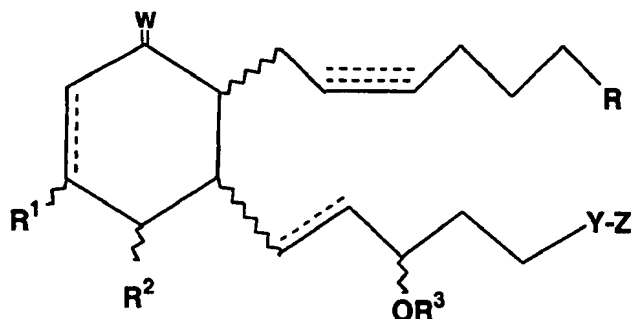
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, R<sup>6</sup> and R<sup>7</sup> forms a condensed aryl ring.

25. The method of claim 24 wherein U is S.
26. The method of claim 25 wherein R is  $\text{CO}_2\text{R}^4$ .
27. The method of claim 26 wherein R is H or methyl.
28. The method of claim 24 wherein Z is phenyl.
- 5 29. The method of claim 28 wherein R is  $\text{CO}^2\text{R}_4$ .
30. The method of claim 29 wherein  $\text{R}^4$  is H.

ABSTRACT OF THE DISCLOSURE

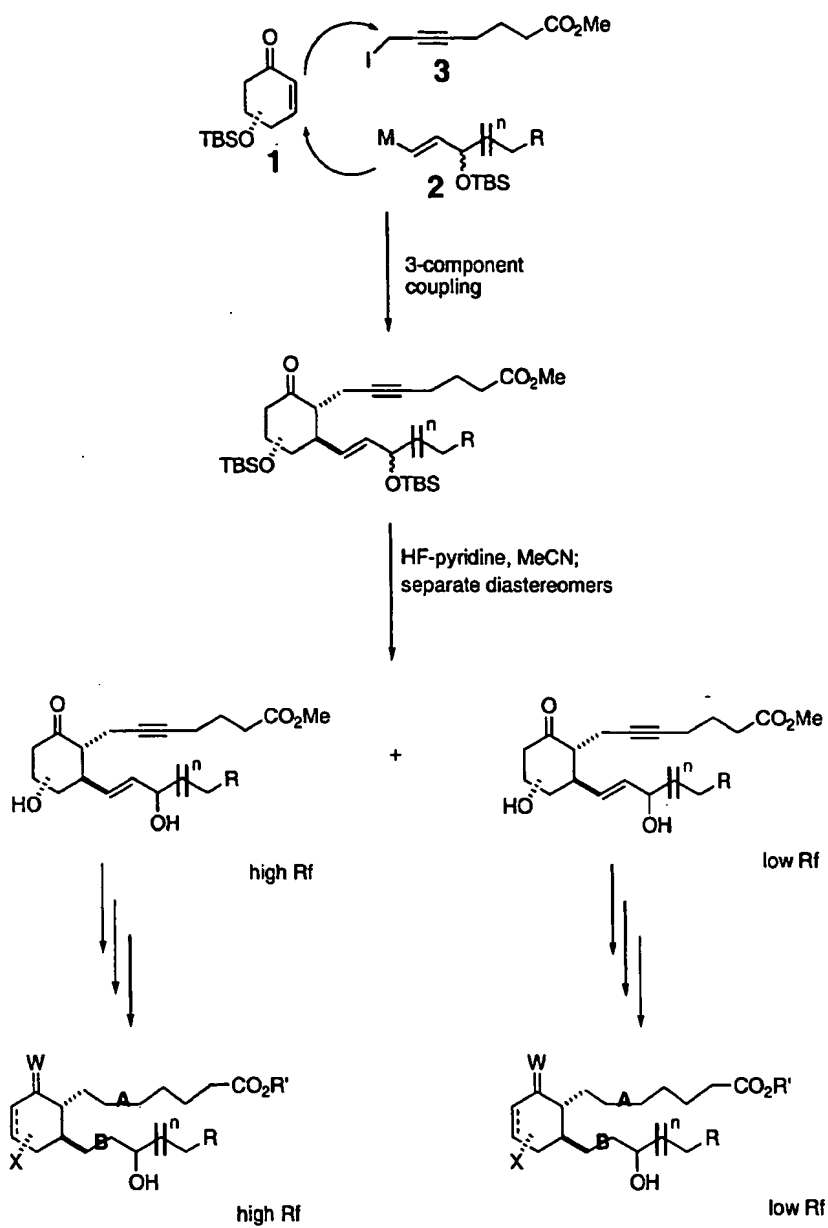
The invention relates to the use of novel cyclohexyl analogues of E-type prostaglandins as EP<sub>4</sub> agonists, in general, and, in particular as ocular hypotensives. The cyclohexyl analogues used in accordance with the invention are represented by the following formula I:



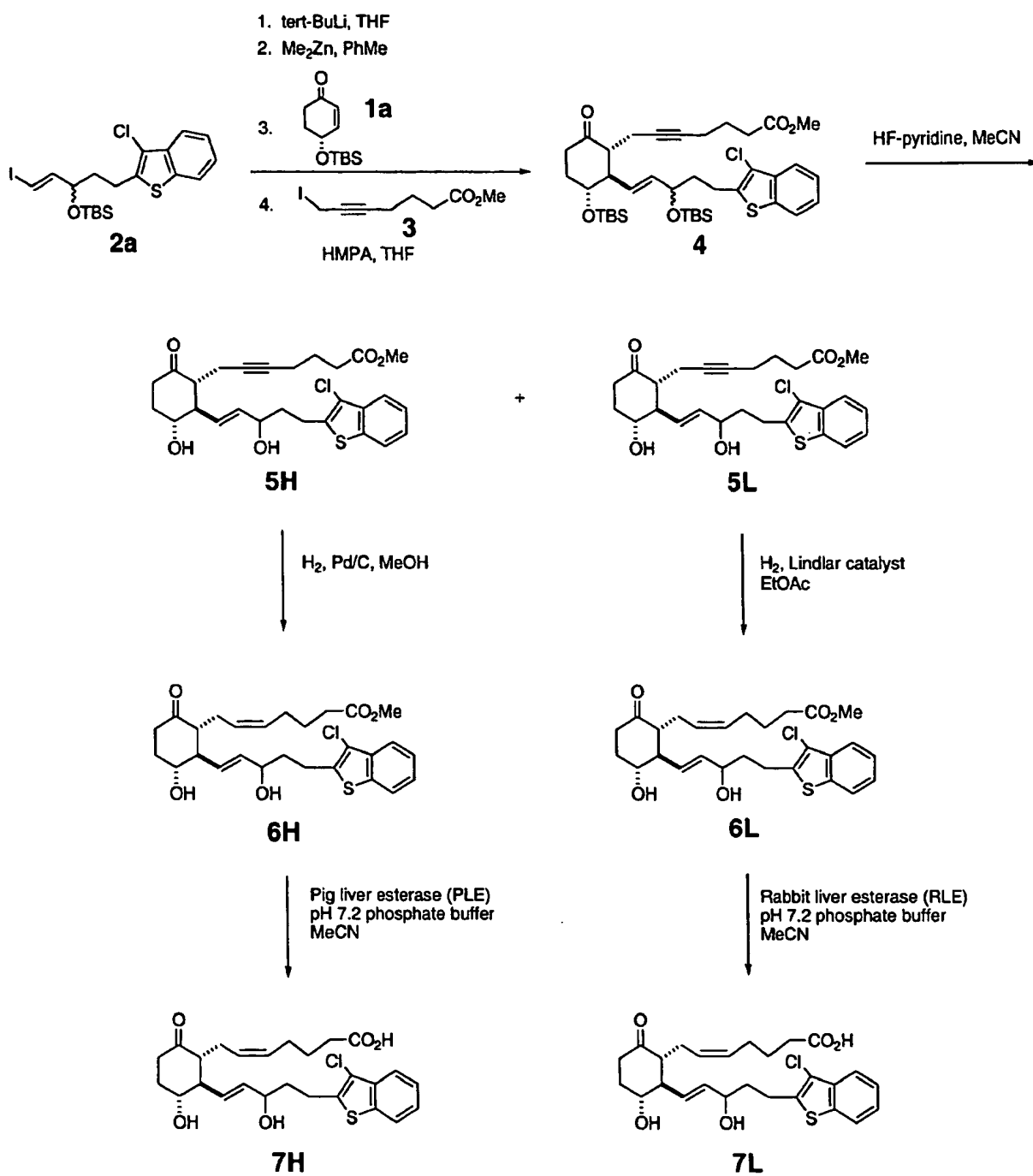
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wherein the wavy segments represent  $\alpha$  or  $\beta$  bond, dashed line represents the presence or absence of a bond W, Y, Z, R, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in the specification.

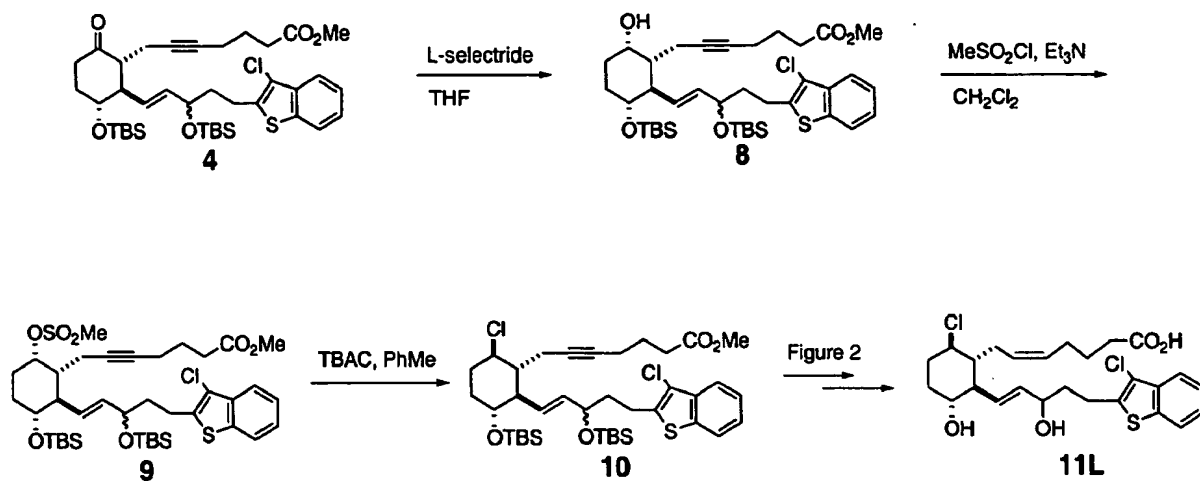
**FIGURE 1**



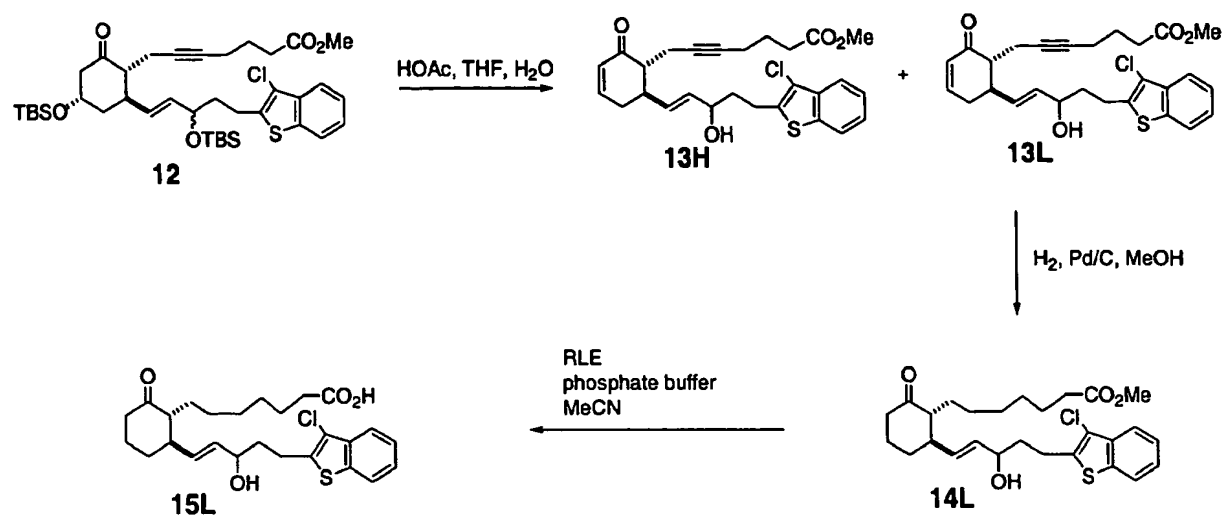
**FIGURE 2**



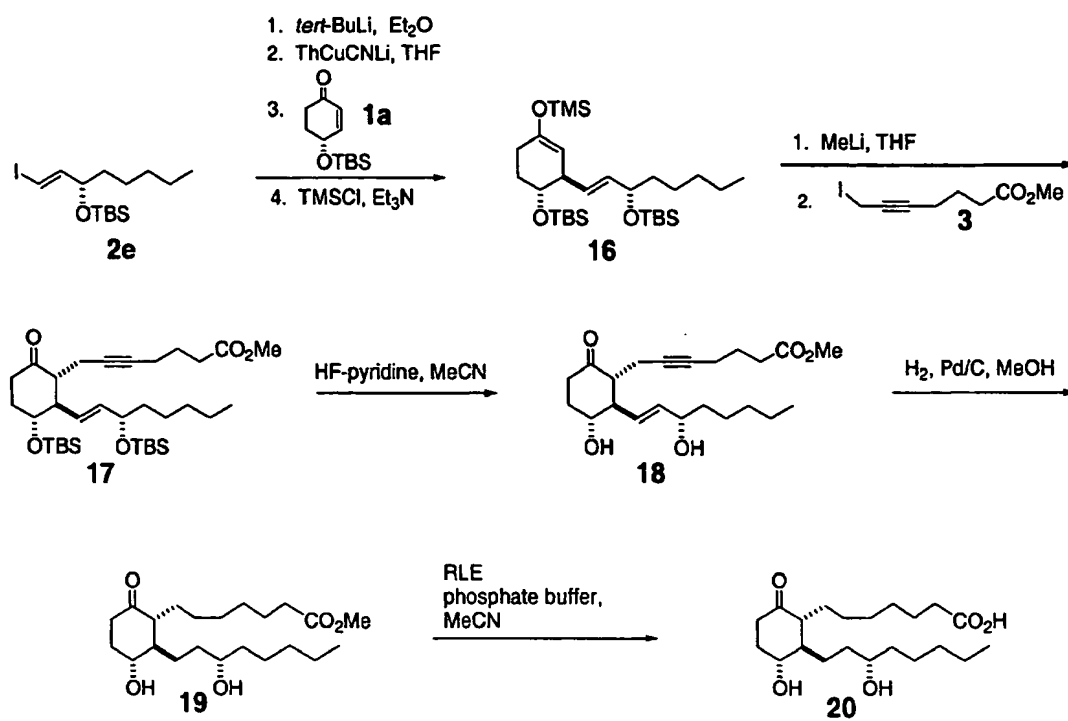
**FIGURE 3**



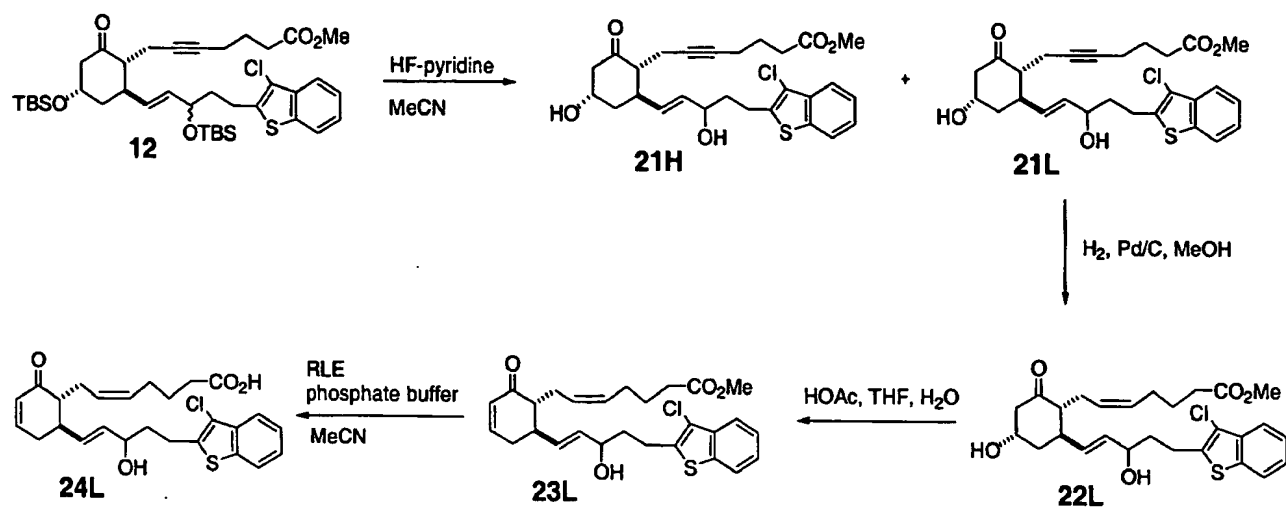
**FIGURE 4**



**FIGURE 5**



**FIGURE 6**



**DECLARATION - U.S.A Application**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled CYCLOHEXYL PROSTAGLANDIN ANALOGS AS EP<sub>4</sub>-RECEPTOR AGONISTS, the specification of which

  x   is attached hereto as Attorney Docket No. 17609 (AP).

       was filed on                      as Application Serial No.  
                     (Attorney Docket No.                     )

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

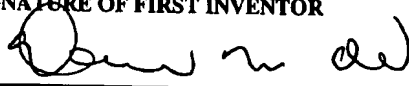
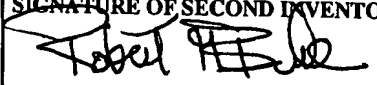
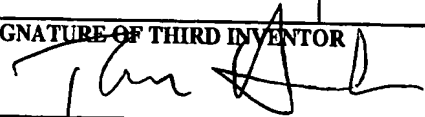
<u>Application No.</u>	<u>Filing Date</u>
------------------------	--------------------

I hereby appoint Robert Baran, Registration No. 25,806, Martin A. Voet, Registration No. 25,208; Carlos A. Fisher; Registration No. 36,510; Stephen Donovan, Registration No. 33,433 and Brent A. Johnson, Registration No. 51,851 as attorneys to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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